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One pot synthesis of 3, 4-dihydropyrimidin - 2(1*H*) - ones catalyzed by aluminium sulphate: An improved procedure for the Biginelli reaction

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ABSTRACT

A simple effective synthesis of 3, 4-dihydropyrimidin-2(1H)-one/thione derivatives using Aluminium sulphate ($Al_2(SO_4)_3{\cdot}18H_2O$) catalyst from aromatic aldehydes, 1, 3-dicarbonyl compounds & (thio)urea in glacial acetic acid is described. Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yield and short reaction time.

Key words: Biginelli reaction, 3, 4-dihydropyrimidin-2(1*H*)-ones, Aluminium sulphate, Condensation reaction, multicomponent reaction.

INTRODUCTION

Development of simple, safe, ecofriendly and economical synthetic routes for widely used organic compounds from the readily available reagents are one of the major challenges in organic synthesis. 3,4- Dihydro -1H pyrimidine-2- thiones/ ones (DHPMs) are among such type of organic compounds which belongs to an important class with significant therapeutic and medicinal properties[1], some of which have antiviral, antitumor, antibacterial and anti-inflammatory activities[2-6].

Several marine alkaloids having the DHPM core unit are showing interesting biological activities such as calcium channel blockers[7, 8], antihypertensive agents, α-adrenergic antagonist and neuropeptide - Y- antagonist[9].

The structurally rather simple than DHPM, monastrol (Fig.1) specifically inhibits the mitotic kinesin Eg5 motor protein and considered as a new lead for the development of anticancer drugs[10, 11].

The batzelladine alkaloids (Fig.1) containing the DHPM core unit inhibit the binding of HIV envelop protein gp-120 to human CD4 cells and therefore, are potential new leads for AIDS therapy[4,12]. Therefore the synthesis of compounds with DHPMs core unit has gained much importance. The most simple and straightforward procedure first reported by Italian chemist Pietro Biginelli in 1893, involves three-component, one pot condensation with â-ketoester with an aldehyde and urea under strongly acidic conditions.[13] One major drawback of this so called Biginelli reaction, however, is the low to moderate yields (20-60 %) that are frequently encountered when using substituted aromatic or aliphatic aldehydes. This has led to development of more complex multistep strategies that produce somewhat higher overall yields but lack the simplicity of the one pot Biginelli protocol.

The art of performing efficient chemical transformation coupling three or more components in a single operation by a catalytic process avoiding

stoichiometric toxic reagents, large amount of solvents and expensive purification techniques represents a fundamental target of modern organic synthesis. Thus Biginelli's reaction for the synthesis of dihydropyrimidinone has received renewed interest and several improved procedures have recently been reported for the preparation of DHPMs based on the modification of classical Biginelli's reaction. These methods have been developed using different Lewis acids such as $AlCl_3$[14], $CuSO_4$[15], $Sr(OTf)_2$[16], $Mn(OAc)_2$[17], $NiSO_4$[18], $InCl_2$[19], BF_3 [20] as well as protic acids, such as H_2SO_4, Conc.HCl as promoters. Several other catalysts, such as iodine[21], NBS[22], Polyphosphate ester[23] have been used to facilitate the reactions. Many other methods including microwave irradiation, ionic liquids, clay, solvent free and catalysts free procedures are also reported. However many of these methods are associated with harsh reaction conditions, expensive and toxic reagents, strongly acidic conditions, tedious workup, stoichiometric amount of catalyst, long reaction times, unsatisfactory yields, incompatibility with other functional groups etc. Therefore, to avoid these limitations, the discovery of a new and efficient catalyst with high catalytic activity, short reaction time, and simple work-up is of prime-interest. In this regard aluminium sulphate octadecahydrate ($Al_2 (SO_4)_3 \cdot 18H_2O$) is a aluminium (III)salt of sulfuric acid (2:3) is used as novel catalyst for the synthesis of DHPMs. Hitherto unused aluminium sulphate is not only very inexpensive, simple, easily available, high yielding (74-93%) but also greatly decreases environmental pollution. & short reaction time (2.5-4 hr)

EXPERIMENTAL

Biginelli reaction between benzaldehyde, ethyl acetoacetate and urea was carried out in the different solvents at variable temperature & catalytic amount. The influence of temperature and various solvents on the formation of product was studied. The reaction was carried out at RT & at refluxing condition except acetic acid (at 80 °C); in the absence and in the presence of solvents the results are compiled in Table.1.

The best results were achieved by carrying out the reaction at 80°C & 10 mol% of catalyst aluminium sulphate in presence of acetic acid as a solvent. No any effect on yield by increasing amount of catalyst. (10 mol% to 20 mol %) Melting point were determined in an open capillary and are uncorrected, Reagent grade chemicals were purchased from commercial source and used as received. IR spectra were recorded on a Perkin-Elmer spectrum on FTIR spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on Varian (300MHz) instrument using DMSO-d_6 as solvent and TMS as an internal reference.

General Experimental procedure for the synthesis of DHPM$_s$

A mixture of aldehyde (2 mmol), 1, 3-dicarbonyl compound (2 mmol), urea/thiourea (2.4 mmol) and Aluminium sulphate (10 mol %) in 10 ml acetic acid was heated at 80^0 C for the appropriate time as mentioned in table 2. After completion of the reaction, as indicated by TLC the reaction mixture poured onto crushed ice (25gm) and stirred for 10 min. Filtered & recrystallised from 95% ethanol & to afford desired DHPMs.

All the products were fully characterized by IR, ^{1}H-NMR & melting points are consistent with the literature data.

Spectroscopic characterization data of DHPMs; 5-Ethoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1*H*)-one, 4a

m.p.200-02^{o}C (lit.[19] m.p. 202-04 ^{o}C); IR. (KBr): 3245, 1725, 1705, 1647cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.12 (s, 1H). 7.66 (s, 1H). 7.28-7.16 (m, 5H), 5.10 (s, 1H), 3.94 (q, *J*=7.1 Hz, 2H), 2.18 (s, 3H), 1.04 (t, *J*=7.1 Hz, 3H).

5-Ethoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-3, 4-dihydropyrimidin-2(1*H*)-one, 4b

m.p. 228-30^{o}C (lit.[23] m.p. 227-29 ^{o}C); IR (KBr): 3355, 3240, 2955, 1710, 1655, 1585 cm^{-1}; ^{1}H NMR δ 9.31 (s, 1H), 9.02 (s, 1H), 7.60 (s, 1H), 7.00 (d, *J*= 6.9Hz, 2H), 6.67 (d, *J*= 6.9Hz, 2H), 5.05 (s, 1H), 3.96(q, *J*= 7.2 Hz, 2H),2.20 (s, 3H), 1.08 (t, *J*= 7.2Hz, 3H).

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3, 4-dihydropyrimidin-2(1*H*)-one, 4c

m.p. 200-02^{o}C (lit.[19] m.p. 201-03 ^{o}C); IR

(KBr): 3225, 1715, 1645, 1612 cm^{-1}; NMR: δ 9.20 (s, 1H), 7.69 (s, 1H), 7.16 (d, *J*=8.6 Hz, 2H), 6.90 (d, *J*=8.6 Hz, 2H), 5.09(s, 1H), 3.99(q, *J*=7.1 Hz, 2H), 3.72 (s, 3H), 2.26 (s, 3H), 1.12 (t, *J*=7.1 Hz, 3H).

5-Ethoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1*H*)-one, 4d

m.p. 216-18°C (lit.[22] m.p. 215-18 °C); IR (KBr): 3225, 1710, 1643, 1560 cm^{-1}; NMR: δ 9.28(s, 1H), 7.73 (s, 1H), 7.21-7.47 (m, 4H), 5.65 (s, 1H), 3.91 (q, *J*=7.1 Hz, 2H),2.29 (s, 1H), 1.08 (t, *J*=7.1 Hz, 3H).

5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1*H*)-one, 4e

m.p. 212-14°C (lit.[19] m.p. 213-15 °C); IR (KBr): 3244, 1712, 1647, 1489 cm^{-1}; NMR: δ 9.20 (s, 1H), 7.76 (s, 1H), 7.40 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J*=8.4 Hz, 2H), 5.11 (s, 1H), 3.96 (q, *J*=7.1 Hz, 2H), 2.23 (s, 3H), 1.06 (t, *J*=7.2Hz, 3H).

5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1*H*)-one, 4f

m.p. 206-08°C (lit.[19] m.p. 208-11 °C); IR (KBr): 3232, 1728, 1643, 1593 cm^{-1}; NMR: δ 9.31 (s, 1H), 8.20 (d, *J*=8.7 Hz, 2H), 7.87 (s, 1H), 7.50 (d, *J*=8.7 Hz, 2H), 5.24 (s, 1H), 3.95 (q, *J*=7.1 Hz, 2H), 2.21 (s, 3H), 1.04 (t, *J*=7.1 Hz, 3H).

5-Ethoxycarbonyl-4-(3-nitrophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1*H*)-one, 4g

m.p. 226-28°C (lit.[18] m.p. 226-27 °C); IR (KBr): 3213, 2962, 1710, 1627, 1581 cm^{-1}; NMR: δ 9.25 (s, 1H), 8.03-8.12 (m, 2H). 7.83 (s, 1H), 7.61-7.72 (m, 2H), 5.30 (s, 1H), 3.97 (q, *J*=7.1 Hz, 2H), 2.51 (s, 3H), 1.07 (t, *J*=7.1 Hz, 3H).

5-Ethoxycarbonyl-4-(2-nitrophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1*H*)-one, 4h

m.p. 210-12°C (lit.[18] m.p. 206-08 °C); IR (KBr):3240, 2980, 1710, 1650, 1580 cm^{-1}; NMR: δ 9.39 (s, 1H), 7.49-7.98 (m, 5H), 5.81 (s, 1H), 3.88(q, *J*=7.5 Hz, 2H), 2.30 (s, 1H), 0.94(t, *J*=7.5Hz, 3H)

5-Ethoxycarbonyl-4-phenyl-6-methyl-3, 4-dihydropyrimidin-2(1*H*)-thione, 4i

m.p. 202-04°C (lit.[23] m.p. 206-08 °C); IR (KBr): 3325, 3171, 1710, 1666, 1573 cm^{-1}; NMR: δ 10.32(s,1H), 9.66(s, 1H), 7.28-7.18(m,5H), 5.19(s, 1H), 3.96(q, *J*= 6.0 Hz, 2H), 2.28(s, 3H), 1.09(t, *J*= 6.0 Hz, 3).

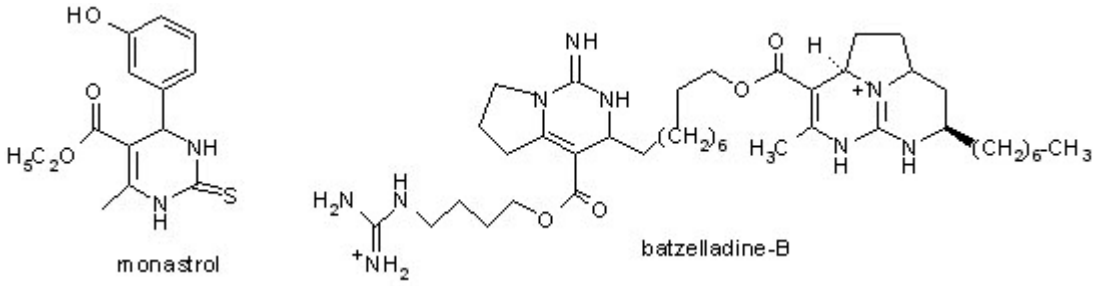
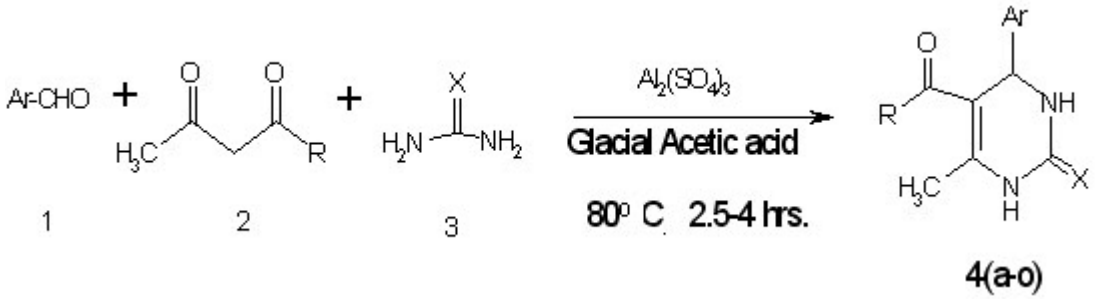


Fig. 1: Examples of biologically active DHPM



General Reaction Scheme

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione, 4j

m.p. 152-54°C (lit.[24] m.p. 150-52 °C); IR (KBr): 3325, 3171, 1710, 1666, 1573 cm^{-1}; NMR: δ 10.31(s, 1H), 9.53(s, 1H), 9.40(s, 1H),7.02(d, *J*=8.4Hz, 2H), 6.67(d, *J*= 8.4 Hz,2H), 4.99(s, 1H), 4.01(q, *J*=7.1Hz,2H), 3.75(s, 3H), 2.29(s, 3H), 1.11(t, *J*=7.1 Hz, 3H).

5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione, 4k

m.p. 182-86°C (lit.[23] m.p. 180-82 °C); IR

Table 1: *Biginelli* reaction using $Al_2(SO_4)_3{\cdot}18H_2O$ in different solvents

Solvent	Stirring at room temperature			Heating at reflux temperature		
	Yield (%)	Time (hr.)	m.p. (°C)	Yield (%)	Time (hr.)	m.p. (°C)
None	43	1.5	198-200	55	1.9	200
Ethanol	38	3.5	202	76	3.0	202
Acetonitrile	46	3.0	200	68	3.5	200
Chloroform	40	4.0	204 -206	56	4.0	198- 200
Toluene	48	3.5	206 -208	74	4.0	202-204
Acetic acid	62	3.0	200 -202	90	3.5	202-204
				88[(a)]	3.0	200-202
				90[(b)]	4.0	204-206
				63[(c)]	4.0	202-204
n-Hexane	44	3.5	198-200	68	4.0	200-202

(a) - Reactions were carried out at 800 C by using 10 mol % catalyst.

(b) - Reaction was carried out at 800C for 4 hrs by using 20 mol%

(c) - Reaction was carried out without catalyst at reflux temp

Table 2: Aluminium sulphate catalyzed synthesis of DHPMs

Entry	Ar-	R-	X	Yield (%)[a]	Time (hr)
4a	C_6H_5-	OEt	O	88	3
4b	4-HOC_6H_4-	OEt	O	86	3.5
4c	4-$MeOC_6H_4$-	OEt	O	80	4
4d	2-ClC_6H_4-	OEt	O	83	3.5
4e	4-ClC_6H_4-	OEt	O	93	4
4f	4-$NO_2C_6H_4$-	OEt	O	82	3.5
4g	4-$NO_2C_6H_4$-	OEt	O	74	4
4h	2-$NO_2C_6H_4$-	OEt	O	78	4
4i	C_6H_5-	OEt	S	90	4
4j	4-$MeOC_6H_4$-	OEt	S	82	4
4k	4-ClC_6H_4-	OEt	S	92	2.5
4l	2-ClC_6H_4-	OEt	S	78	4
4m	C_6H_5-	Me	O	76	2
4n	4-$NO_2C_6H_4$-	Me	O	82	4
4o	4-$MeOC_6H_4$-	Me	O	78	4

a= isolated yield

(KBr): 3329, 3174,1715,1674, 1573 cm^{-1}; NMR: δ 10.38(s,1H), 9.65(s, 1H), 7.45(d, *J*=8.4Hz, 2H), 7.22(d, *J*=8.4Hz, 2H), 5.19(s, 1H), 3.98(q, *J*=7.1Hz, 2H), 2.31(s, 3H), 1.08(t, *J*=7.1Hz, 3H).

5-Ethoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione, 4l

m.p. 200-04°C (lit.[23] m.p. 203-05 °C); IR (KBr): 3178,1712, 1651, 1573 cm^{-1}; NMR: δ 10.35(s, 1H), 9.62(s, 1H), 7.41-7.43(m, 1H),7.23-7.38(m, 3H), 5.61(s, 1H), 3.96(q, *J*=7.1Hz, 2H),2.33(s, 3H),1.07(t, *J*=7.1Hz, 3H).

5-Acetyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4m

m.p. 231-33°C (lit.[24] m.p. 233-36 °C); IR (KBr):3255, 1702, 1665, 1596 cm^{-1}; NMR: δ 9.19(s, 1H), 7.82(s, 1H), 7.30-7.17(m, 5H), 5.24(s, 1H), 2.28(s, 3H), 2.08(s, 3H).

5-Acetyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4n

m.p. 228-30°C (lit.[24] m.p. 230 °C); IR (KBr): 3236, 2951,1728, 1666, 1620 cm^{-1}; NMR: δ 9.28(s, 1H), 8.26 (d, *J*=8.7 Hz, 2H), 7.84 (s, 1H), 7.50 (d, *J*=8.7 Hz, 2H), 5.24 (s, 1H), 2.32(s, 3H), 2.21 (s, 3H),

5-Acetyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, 4o

m.p. 170-72°C (lit.[16] m.p. 168-170 °C); IR (KBr): 3228, 1697, 1631,1593 cm^{-1}; NMR: δ 9.15(s, 1H), 7.67(s, 1H), 7.21(d, *J*=8.3 Hz, 2H), 6.82(d, *J*=8.3 Hz, 2H), 5.16(s, 1H), 3.67(s, 3H), 2.22(s, 3H), 2.10(s, 3H),.

RESULTS AND DISCUSSION

According to the above experimental section, we discovered a practical and general approach for this *Biginelli* cyclocondensation reaction using a mild catalyst aluminium sulphate

Octadecahydrate, which is not only preserved the simplicity of *Biginelli's* one pot reaction but also consistently procedure 74-93% yields of the 3,4-dihydropyrimidin-ones or thions.

In order to study the generality of this procedure a series of *Biginelli* compounds were synthesized with similar operations. Under these novel conditions, the reaction time was significantly shorted from 18 hr to the classical Biginelli method to 2-4.5 hr, and the yields increased from 20-50% to 74-93%. Most importantly, aromatic aldehydes carrying either electron donating or withdrawing substituents afforded good yields of products. Furthermore thiourea has been used with similar success to provide the corresponding good biological activities. In order to get the best molar ratio of reaction materials, we also the experiment with different ratios of aldehydes (1), 1-3dicarbonyl compound (2), urea or thiourea (3) and Aluminium sulphate. We found that the reaction gave the best results, when the molar ratio of reactants was (1) 1: (2) 1: (3) 1.2 & 10 mol% of catalyst w.r.t-(1) respectively.

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